The Evolutionary Histories of Cancers

Jeffrey Townsend, PhD

A group of Yale scientists are using the tools of evolutionary biology to study cancer, with surprising results. A paper published last year [ed.--2017] in the *Proceedings of the National Academy of Sciences* demonstrated that these tools can transform our basic understanding of how cancer begins and spreads, and also can help researchers prioritize targets for attack.

The study's main author is Jeffrey Townsend, PhD, Elihu Associate Professor of Biostatistics and of Ecology and Evolutionary Biology, and Director of Bioinformatics at the Yale Center for Analytical Sciences. An evolutionary biologist, Dr. Townsend turned his attention to cancer a few years ago because he saw an opportunity to harness well-established principles from his field to enable new technologies and expand the impact of cancer databases.

"With high throughput sequencing," said Dr. Townsend, "we now can sequence the whole exomes of different cancers, both primary tumors and metastases. Until recently we couldn't get enough data to do that. Now we can begin to infer how the expressed genomes of the cancers at different tissue sites are related to each other."

To do this, he uses a tool that evolutionary biologists call molecular evolutionary models. These models compare sequences of DNA from different organisms to discover how and when the organisms diverged, which also reveals how closely or distantly they are related. A second tool, "reconstructed ancestral states," uses DNA sequencing to trace how a gene evolved, which enables evolutionary biologists to extrapolate the gene's ancestral states along an evolutionary timeline.

He and his team performed whole exome sequencing of autopsy samples archived at Yale from 40 people with 13 types of cancer. They sequenced samples from normal tissue, 32 primary tumors, and 139 sites of metastases. Many of the samples were taken at multiple points during a patient's treatment, which allowed the scientists to construct a timeline of the cancers' emergence and evolution, and to detect the cancers' genetic origins and relationships to each other. The findings have upended some assumptions.

First, Dr. Townsend produced family trees for each tumor and its metastases. "If all the metastases had a common genetic origin within the primary tumor," he said, "they would have only brother-sister relationships with other metastases. That wasn't true." Instead, he found that the metastases often diverged genetically from the primary tumor very early in the tumor's history, in some cases even before the primary tumor had been diagnosed. This early divergence contradicts what Dr. Townsend calls "the longstanding linear model of cancer progression," which holds that mutations lead to cell proliferation that causes a primary tumor, followed by mutations that explode into metastases.

"That model assumes all metastases would be related," said Dr. Townsend. "But when you see metastases being quite divergent from each other and from the primary tumor, very early in the primary tumor, I would say that our results put the final 'nail in the coffin' of linear thinking about cancer."

This has important implications for treating cancer. A patient often follows a familiar sequence: diagnosis of a primary tumor, remission, recurrence with metastases, and treatment of the metastases. Using targeted therapy against the primary tumor may not touch less genetically-related metastases within the tumor, so they pop up later.

This insight led to another third important finding: after reconstructing the tumors' ancestral states, Dr. Townsend and his colleagues noted two well-known genes that repeatedly mutated early in the evolution of all the primary tumors and metastases—the oncogene KRAS and the tumor suppressor TP53. Both are known cancer drivers, but the hard evidence provided by his analyses makes their early evolutionary role news. The frequent presence of these well-known culprits in the genetics of cancer at the root of diverse cancer lineages, the authors wrote, "implies that they play key formative roles in the origin of cancer and that they deserve redoubled attention for their roles in tumorigenesis."

Dr. Townsend notes that no good drugs currently exist against KRAS and TP53, though some for KRAS are in the pipeline. "The mutations that happen very early are where we should put our effort in the design and development of new drugs," he said, "because anything that addresses the genesis of cancer will address later cancers as well. We have to figure out how we can corner the cancer—and destroy all of it—instead of destroying just one part and allowing the other parts to develop resistance."

Dr. Townsend hopes to perform further studies on samples of many cancers taken from living patients to learn how and when each type develops and evolves. "Evolutionary biology can help us understand each cancer's life history," he said, "and from that can come a strategy for treating them."